DETAILED ACTION

Status of the claims

Applicant's amendment filed 07/22/09 is acknowledged and has been entered. Claims 1-12 have been cancelled. Claims 13-20 have been added. Accordingly, claims 13-20 are pending and are under examination.

Withdrawn Rejections

All rejections of claims not reiterated herein, have been withdrawn.

The rejections of claims 1-9 are now moot in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 13-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13, line 1 the recitation "early determination of risk" is vague and indefinite because the term "early" is a relative term which renders the claim indefinite. The phrase "early determination of risk" is not defined by the claim, the specification does

not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 16 is vague and indefinite in reciting an open ended range of the cutoff in reciting "310 ng/ml or more." Such open-ended range appears to encompass infinite levels of the cutoff level for application in the claimed method.

Claim 18, line 4 is indefinite in reciting improper Markush language in reciting. "soluble cytokeratin fragments selected from" because it appears to intend to limit the scope of the soluble cytokeratin fragments in the claims but improperly defines it as such. Perhaps, Applicant intends "soluble cytokeratin fragments selected from the group consisting of."

Claim 18, lines 7- 8 is indefinite in reciting improper Markush language in reciting. "peptide prohormones selected from" because it appears to intend to limit the scope of the peptide prohormones in the claims but improperly defines it as such. Perhaps, Applicant intends "peptide prohormones selected from the group consisting of."

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 13-15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Warner et al (Clin. Chemistry 41/6, pgs 867-871, 1995) and Galikowski et al (Research in Surgery, Vol. 6, No. 1, April 1994) in view of Uda et al (EP 0217542).

Warner et al disclose a method for the determination of risk of mortality of patients in intensive care units (e.g. Abstract, col. 2 (Materials and Methods)). Warner et al disclose determining enzyme concentrations of superoxide dismutase (SOD) in plasma samples obtained from septic patients. According to Warner et al., the superoxide dismutase consists of three isoforms, including SOD1 (Cu/Zn SOD), SOD2

and SOD3). Warner et al. teach comparing the concentrations to a predetermined cut-off and determining increases for prognosis (e.g. Abstract, p. 869-871). Warner et al also teach that catalase (sepsis prognosis marker) is increased in sepsis and is determined along with SOD

Warner et al differ from the instant invention in failing to teach determining the concentration of SOD-1 (Cu/Zn SOD) in the sample.

Galikowski et al teach that SOD1 activity is increased during sepsis.

Uda et al teach that the concentration of SOD1 (Cu/Zn SOD) can be determined in patient samples by means of immunoassays. Uda et al. also teach that the immunoassays comprise antibodies specific for SOD1 and can be an ELISA assay utilizing monoclonal antibodies. The ELISA assay utilizes at least one labeled (marked) antibody. Uda et al also teach that the amount of SOD-1 in a patients sample can be detected with good precision and with extremely high specificity and used in diagnostic methods.

Although Warner et al. does not specifically teach determining the concentration of SOD1, Warner does teach that SOD1 is included in the increased enzyme activity of SOD during sepsis and Galikowski et al teach that it is known that SOD1 activity is increased during sepsis. Therefore, as shown by Galikowski et al the increased enzymatic activity of Warner et al would include increase activity of SOD1. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the determination of the concentration of SOD1 as taught by Galikowski in the method of Warner et al because Uda et al taught that it is

known that SOD1 concentrations can be determined in patient samples with good precision and with extremely high specificity and used in diagnostic methods such as taught in both Warner and Galikowski.

7. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Warner et al., Galikowski et al in view of Uda et al as applied to claims 1-3 and 5 above, and further in view of Valkirs et al (US 2003/0119064).

See above for the teachings of Warner et al., Galikowski et al and Uda et al.

Warner et al., Galikowski et al and Uda et al differ from the instant invention in failing to explicitly teach the cutoff level of 310 ng/ml or more.

Valkirs et al teach that it is known in the art to use ROC curves and to established cut-off levels and particularly teach that for any particular marker, a distribution of marker levels for subjects with and without a disease will likely overlap and that under such conditions, a test does not absolutely distinguish normal from disease with 100% accuracy, and the area of overlap indicates where the test cannot distinguish normal from disease. Valkirs et al also teach that a threshold is selected, above which (or below which, depending on how a marker moves with the disease) the test is considered to be abnormal and below which the test is considered to be normal.

It would have been obvious to one of ordinary skill in the art to incorporate ROC curves and determine the optimum threshold level as taught by Valkirs et al with the modified method of Warner et al because the modified method of Warner specifically taught cut-offs and Valkirs et al showed that it is known in the art that for any particular marker, a distribution of marker

levels for subjects with and without a disease will likely overlap and that under such conditions, a test does not absolutely distinguish normal from disease with 100% accuracy, and the area of overlap indicates where the test cannot distinguish normal from disease.

With respect to the 310 ng/ml cutoff as recited in the instant claims, the optimum cutoff level can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. Further, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation ." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

8. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Warner et al., Galikowski et al in view of Uda et al as applied to claims 1-3 and 5 above, and further in view of Bohuon (US 5,639,617).

See above for the teachings of Warner et al., Galikowski et al and Uda et al.

Warner et al., Galikowski et al and Uda et al differ from the instant invention in failing to teach that the further marker is procalcitonin.

Bohuon teaches a method for early detection, detection of the severity and for a treatment-accompanying assessment of the course of a sepsis, as well as means for carrying out such a method using procalcitonin and/or partial peptides thereof in a biological sample of a patient along with the simultaneous determination of calcitonin using immunological procedures using specific antibodies (e.g. abstract, cols 3-5, examples 1-3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the more established parameters of sepsis such as procalcitonin as taught by Bohuon with the modified method of Warner et al because the determination of procalcitonin would provide for further confirmation of sepsis and severity of sepsis.

9. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Warner et al., Galikowski et al., Uda et al in view of Bohun as applied to claims 1-3, 5 and 6 above, and further in view of Wagner et al (US 6,329,209).

See above for the teachings of Warner et al., Galikowski et al., Uda et al and Bohun.

Warner et al., Galikowski et al., Uda et al and Bohun differ from the instant invention in failing to teach the simultaneous determination by means of a chip technology and evaluating the results obtained with the aid of a computer program.

Wagner et al disclose arrays and methods for determining analytes in a sample (e.g. Abstract, col. 2-3, col 9-11, col. 32-36). Wagner et al disclose that the arrays can

be chips (e.g. col 2, example 1). Wagner et al disclose that arrays are used in immunoassays and detection and evaluation of the results is performed with the aid of a computer (e.g. col 34-35). Wagner et al. also teach that this provides for methods to be performed in parallel (col 3). Wagner et al. teach that this protein array provides the advantage of simultaneously detecting a plurality of proteins in a sample and also provides methods for multianalyte analyses (abstract & col 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate chip arrays and computers as taught by Wagner et al into the modified method of Warner et al because Wagner et al taught that this provides for methods to be performed in parallel. Wagner also taught that this protein array provides the advantage of simultaneously detecting a plurality of proteins in a sample and also provides methods for multianalyte analyses.

10. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Warner et al., Golikowski et al and Uda et al as applied to claims 1-3, and 5 above, and further in view of Daniels et al (US 2006/0008921).

See above for the teachings of Warner et al., Golikowski et al and Uda et al.

Warner et al., Golikowski et al and Uda et al differ from the instant invention in failing to teach performing the detection with immunochromatographic point-of-care.

Daniels et al teach immunochromatgraphic test strips and methods for quantifying an analyte of interest in a sample (e.g. abstract, pages 2-4). Daniels et al teach that immunochromatographic lateral flow or strip tests are well-established

diagnostic tools for detecting analytes (para. 0003). Daniels et al teach that test strips offer the advantages of a simple, user-friendly format, and rapidly obtained results that are easily interpreted and are well suited for applications such as rapid point-of-care testing (para. 0004).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate immunochromatographic devices such as taught by Daniels et al into the modified method of Warner et al because Daniels et al teaches that immunochromatographic lateral flow or strip tests are well-established diagnostic tools for detecting analytes and that test strips offer the advantages of a simple, user-friendly format, and rapidly obtained results that are easily interpreted and are well suited for applications such as rapid point-of-care testing.

Response to Arguments

11. Applicant's arguments filed 07/22/09 have been fully considered but they are not persuasive.

112 2nd rejections

Applicant argues that early diagnosis or early determination of risk would have a clear meaning to a person of ordinary skill in the art and directs the Examiner's attention to paragraphs [0009], [0023], [0026], and [0027] and states that the application discloses "early stage" of a sepsis…early diagnosis of a sepsis.. and early distinction between a sepsis due to infection and severe inflammations..".

This is not found persuasive because although the specification might disclose the terms "early stage of a sepsis...early diagnosis of a sepsis and early distinction. The specification does not specifically provide a definition for the phrase as recited in the current method claims nor does the specification provide specific guidance on what is considered to be early determination of the risk of mortality of patients in intensive care units. Therefore, it is unclear what the phrase encompasses and one would not be reasonably apprised of the scope of the invention.

Applicant argues that 310 ng/ml or more is clear and particularly points out and distinctly claims the subject matter.

This is not found persuasive because of reasons stated above and further because the phrase "or more" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "or more" thereby rendering the scope of the claim unascertainable See MPEP § 2173.05(d).

103 rejections

Applicant argues that it would not have been obvious to one of ordinary skill in the art to combine Warner and Galikowski in view of Uda because Warner discloses determining general SOD activity (total plasma SOD) by an assay which does not distinguish between the three known isoforms of SODs and that Galikowski does not remedy the deficiencies of Warner, and Uda fails to even disclose linking SOD-1 concentrations in blood of sepsis patients with their mortality risk.

This is not found persuasive because the Examiner has not relied upon Warner for teaching determining the concentration of SOD-1 but rather as stated above has relied upon Warner for teaching that SOD1 is included in the increased enzyme activity of SOD during sepsis and has relied upon Galikowski for teaching that it is known in the art that SOD1 activity is increased during sepsis. Further, with respect to Uda, the Examiner has not relied upon Uda for linking SOD1 concentrations in blood of sepsis patients with their mortality risk but rather has relied upon Uda for teaching it is known that SOD1 concentrations can be determined in patient samples with good precision and with extremely high specificity and used in diagnostic methods. Thus it appears that the Applicant is arguing the references individually and in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Therefore, although Warner et al does not specifically teach determining the concentration of SOD1, Warner does teach that SOD1 is included in the increased enzyme activity of SOD during sepsis and Galikowski et al teach that it is known that SOD1 activity is increased during sepsis. Therefore, as shown by Galikowski et al the increased enzymatic activity of Warner et al would include increase activity of SOD1. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the determination of the concentration of SOD1 as taught by Galikowski in the method of Warner et al because Uda et al taught that it is known that SOD1 concentrations can be

determined in patient samples with good precision and with extremely high specificity and used in diagnostic methods such as taught in both Warner and Galikowski.

Conclusion

12. No claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GARY W. COUNTS whose telephone number is (571)272-0817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ Gary W. Counts/
Examiner, Art Unit 1641

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

10/24/09